A Mathematical Approach to Uncertainty in the Parameters for the Regulation of Factor Xa Formation by the Inhibitor TFPI

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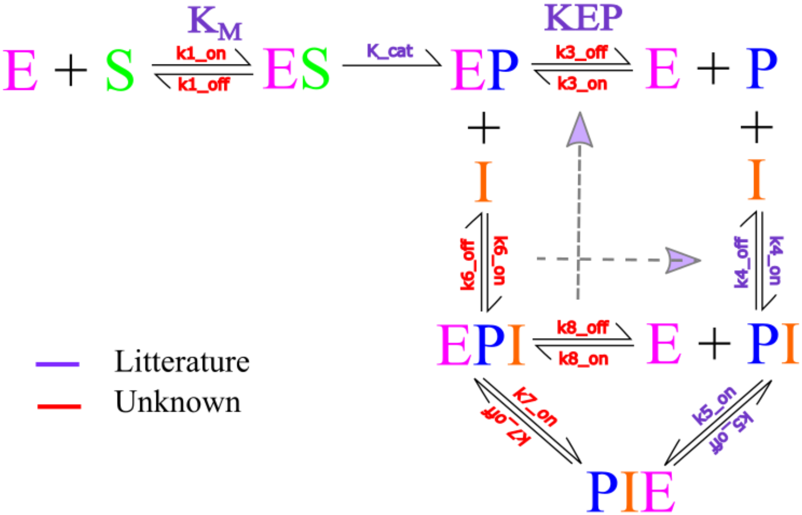
Goals

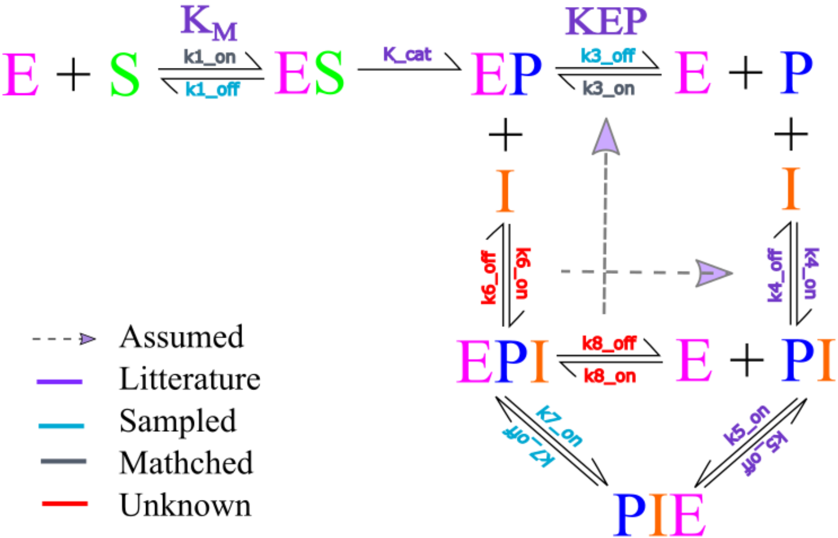
- make a new scheme diagram
- Compute the error and make histogram of error for various samples.
- Heat Map K3on, K7on. (the other values fix at their optimal)
- Fix $k3_o ff \in [100, 200]$ and then run the experiment suggested by professor Karin.
- Add uncertainty $\pm 10\%$ to Karin's parameters and propagate the uncertainty in the model and see what is the best fit.
- Add noise for K_{cat}.
- find the parameters which fit the data properly.

Flowchart



K_M
KEP
E + S
k1_on
k1_off
ES
K_cat
EP
k3_off
k3_on
E + P
+
I
k6_off
k6_on
k4_off
k4_on
EPI
k8_off
k8_on
E + PI
k7_on
k7_off
k5_on
k5_off
PIE
Litterature
Unknown

Flowchart



KM
E + S
k1_on
k1_off
ES
K_cat
KEP
EP
k3_off
k3_on
E + P
+
I
+
I
k6_off
k6_on
k4_off
k4_on
EPI
k8_off
k8_on
E + PI
k7_on
k7_off
k5_on
k5_off
PIE
Assumed
Litterature
Sampled
Mathched
Unknown

Parameters Used for Experiment I.

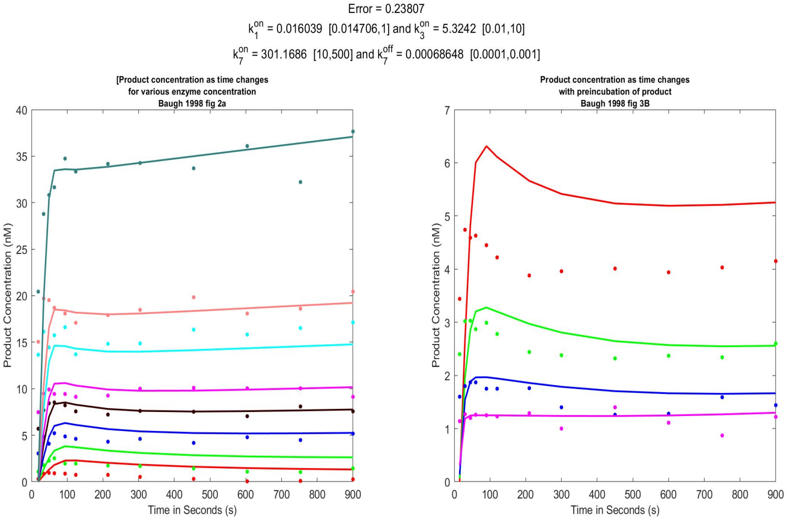
	Units	Amandeep (both exp)	Karin	Baugh
K_M	nM	238	238	238
k_1^{ON}	$(nMs)^{-1}$	$0.016039 \in [k_2/K_M, 1]$	0.189	None
k_1^{OFF}	s^{-1}	0.3173	1	None
k_{cat}	s^{-1}	3.5	3.5	7
$K_{E,P}$	nM	520	520 (LU paper)	NA
k_3^{ON}	$(nMs)^{-1}$	$5.3242 \in [0.01, 10]$	0.3462	NA
k_3^{OFF}	s^{-1}	$2.7686e+03$	180	NA
k_4^{ON}	$(nMs)^{-1}$	0.9×10^{-3}	0.9×10^{-3}	0.9×10^{-3}
k_4^{OFF}	s^{-1}	3.6×10^{-4}	3.6×10^{-4}	3.6×10^{-4}
k_5^{ON}	$(nMs)^{-1}$	7.34×10^{-3}	7.34×10^{-3}	7.34×10^{-3}
k_5^{OFF}	s^{-1}	11×10^{-4}	11×10^{-4}	11×10^{-4}
k_6^{ON}	$(nMs)^{-1}$	k_4^{ON}	1	NA
k_6^{OFF}	s^{-1}	k_4^{OFF}	10^{-3}	NA
k_7^{ON}	s^{-1}	$301.1686 \in [10, 500]$	1000	NA
k_7^{OFF}	s^{-1}	$0.00068648 \in [10^{-4}, 10^{-3}]$	0.0001	NA
k_8^{ON}	$(nMs)^{-1}$	k_3^{ON}	$k_3^{ON} = 0.3462$	NA
k_8^{OFF}	s^{-1}	k_3^{OFF}	$k_3^{OFF} = 180$	NA

Note: $k_6^{ON} = k_4^{ON}$, $k_6^{OFF} = k_4^{OFF}$, $k_8^{ON} = k_3^{ON}$ and $k_8^{OFF} = k_3^{OFF}$ are assumed to be same because it is the same physical binding.

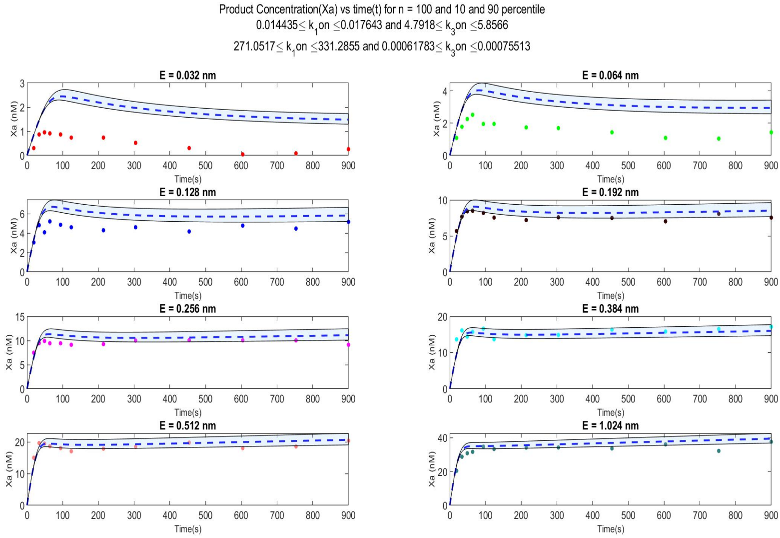
i	Reaction	$K_i = k_{off}/k_{on}$	Aman	Karin
1	$E + S \rightleftharpoons ES$	K_1	19.7830	5.2910
2	$ES \rightharpoonup EP$	-	-	-
3	$E + P \rightleftharpoons EP$	K_3	520.0030	519.9307
4	$P + I \rightleftharpoons PI$	K_4	0.4	0.4
5	$E + PI \rightleftharpoons PIE$	K_5	0.1499	0.1499
6	$EP + I \rightleftharpoons EPI$	$K_6 = K_4$	0.4	1e-03
7	$EP\text{-}I \rightleftharpoons PIE$	K_7^*	2.2794e-06	1e-07
8	$E + PI \rightleftharpoons EP\text{-}I$	$K_8 = K_3$	520	519.9307

(*): does not follow the units for dissociation constant K_d.

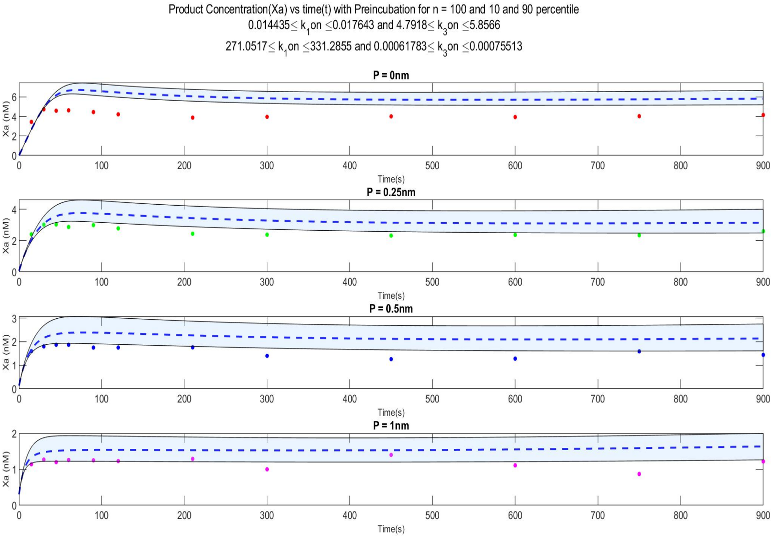
Optimization of k_1^{on}, k_3^{on}, k_7^{on}, and k_7^{off}



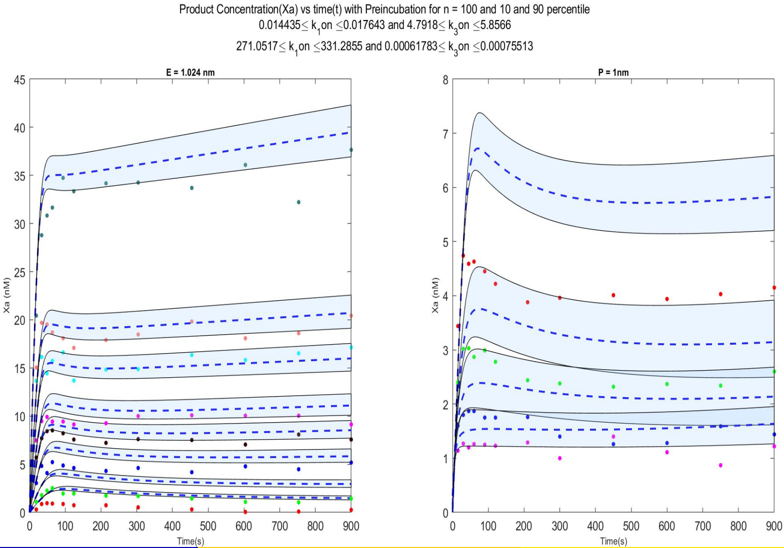
LHS with ±10% Uncertainty: Enzyme Varing Experiment



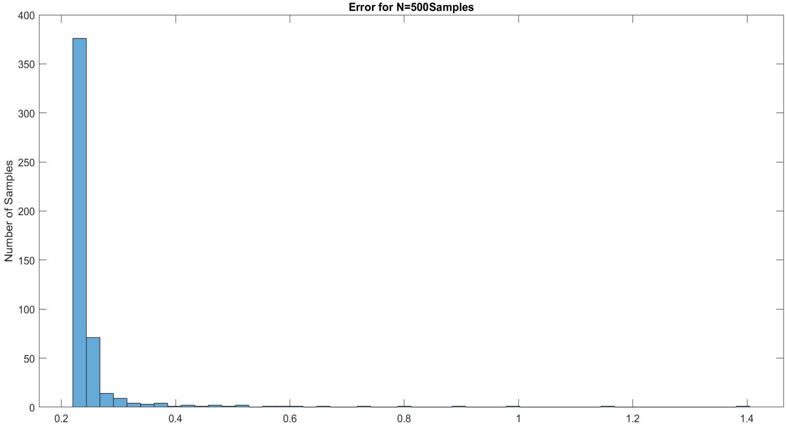
LHS with ±10% Uncertainty for Pre-incubation Experiment



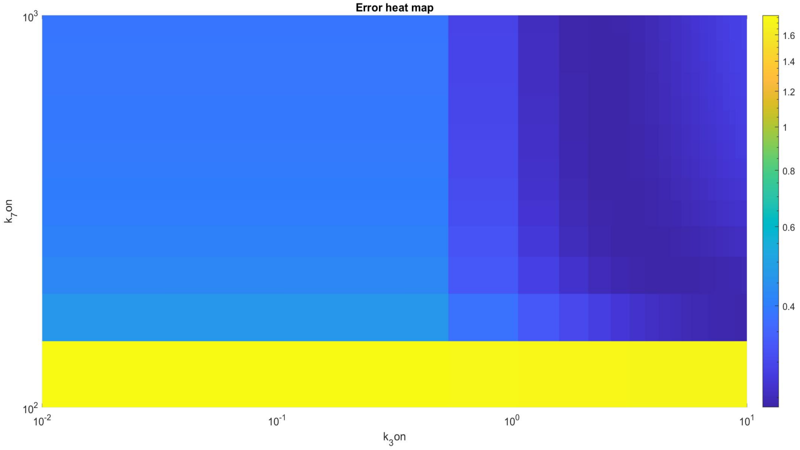
LHS with ±10% Uncertainty for Both Experiment



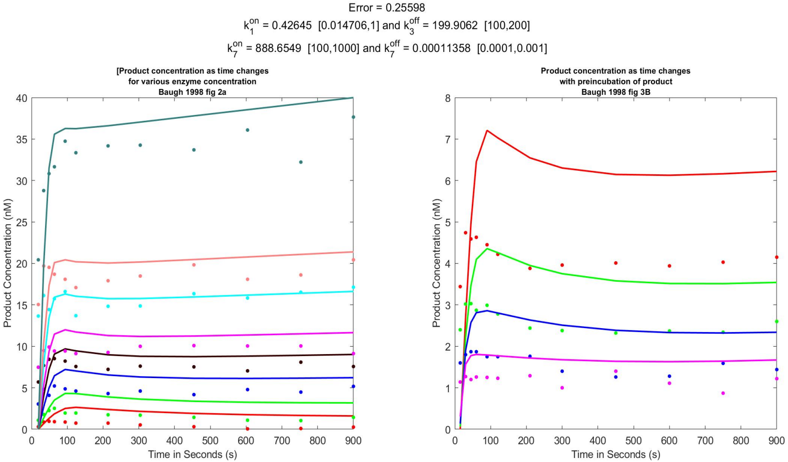
Histogram of Error computed for each sample with N=500 samples



Heat map for k_3on vs k_7on



Fix $k_3off \in [100, 200]$ instead of k_3on

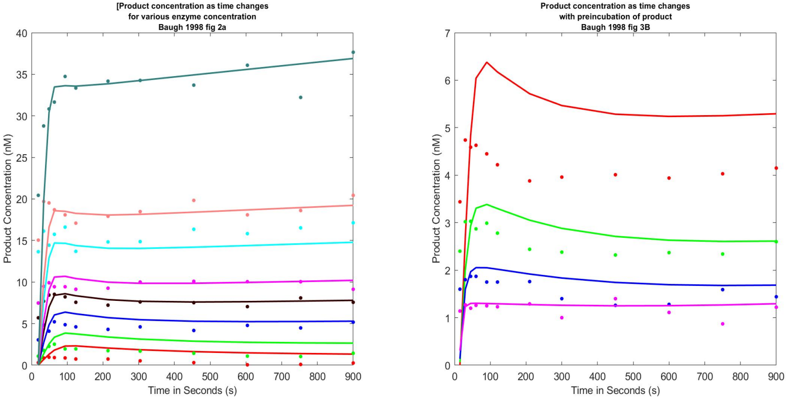


LHS sampling $\pm 10\%$

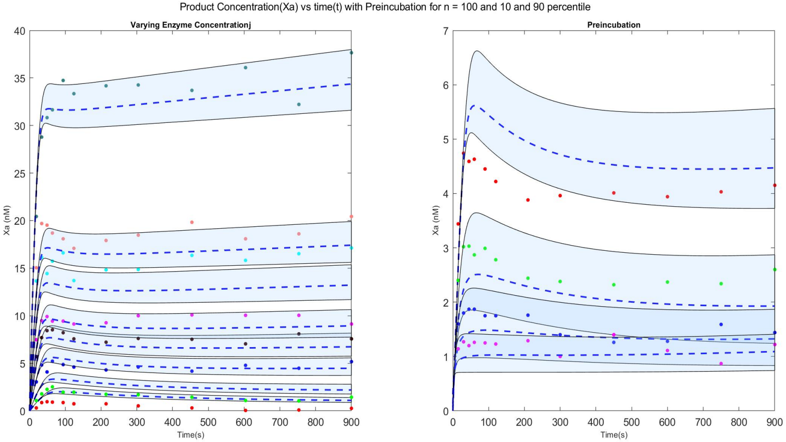
Error = 0.23775

k_1^{on} = 0.81013 [0.014706,1] and k_3^{off} = 365.4251 [100,500]

k_7^{on} = 841.2395 [100,1000] and k_7^{off} = 0.001398 [0.0005,0.005]



Fix $k_3 off \in [100, 500]$ instead of $k_3 on$

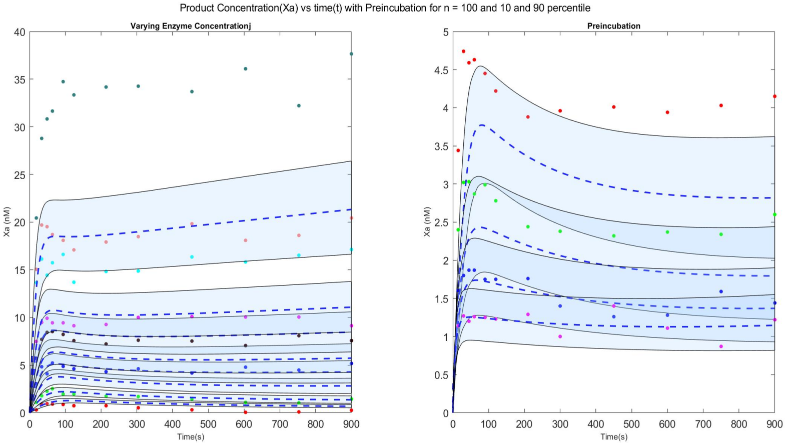


Parameters Used for Experiment I.

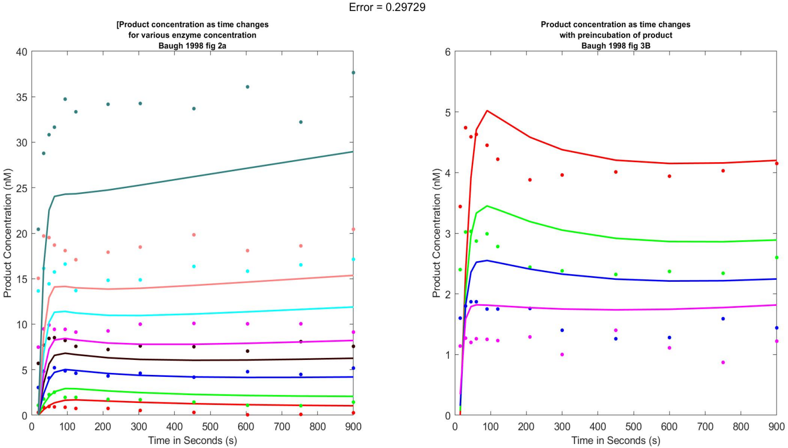
	Units	Amandeep	Karin	Baugh
K_M	nM	238	238	238
k_1^{ON}	$(nMs)^{-1}$	$0.81013 \in [k_2/K_M, 1]$	0.189	None
k_1^{OFF}	s^{-1}	189.31	1	None
K_{cat}	s^{-1}	3.5	3.5	7
$K_{E,P}$	nM	520	520 (LU paper)	NA
k_3^{ON}	$(nMs)^{-1}$	0.70274	0.3462	NA
k_3^{OFF}	s^{-1}	$365.43 \in [100, 500]$	180	NA
k_4^{ON}	$(nMs)^{-1}$	0.9×10^{-3}	0.9×10^{-3}	0.9×10^{-3}
k_4^{OFF}	s^{-1}	3.6×10^{-4}	3.6×10^{-4}	3.6×10^{-4}
k_5^{ON}	$(nMs)^{-1}$	7.34×10^{-3}	7.34×10^{-3}	7.34×10^{-3}
k_5^{OFF}	s^{-1}	11×10^{-4}	11×10^{-4}	11×10^{-4}
k_6^{ON}	$(nMs)^{-1}$	k_4^{ON}	1	NA
k_6^{OFF}	s^{-1}	k_4^{OFF}	10^{-3}	NA
k_7^{ON}	s^{-1}	$841.24 \in [100, 1000]$	1000	NA
k_7^{OFF}	s^{-1}	$0.001398 \in [5 * 10^{-4}, 5 * 10^{-3}]$	0.0001	NA
k_8^{ON}	$(nMs)^{-1}$	k_3^{ON}	$k_3^{ON} = 0.3462$	NA
k_8^{OFF}	s^{-1}	k_3^{OFF}	$k_3^{OFF} = 180$	NA

Note: $k_6^{ON} = k_4^{ON}$, $k_6^{OFF} = k_4^{OFF}$, $k_8^{ON} = k_3^{ON}$ and $k_8^{OFF} = k_3^{OFF}$ are assumed to be same because it is the same physical binding.

LHS with ±10% Uncertainty for Both Experiment using Karin's parameters



Optimization of all the Karin's parameters using $\pm 10\%$ range



Optimized parameter values for Karin parameters

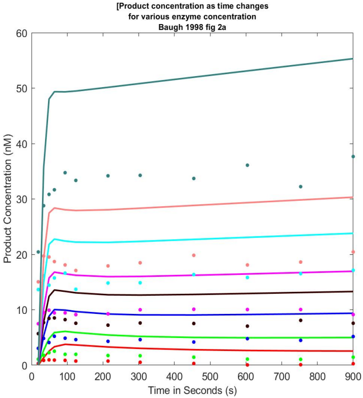
parameter	optimized value
K_M	238
$k_1 on$	0.017289
$k_1 off$	0.90572
K_{cat}	3.85
$K_{E,P}$	520
$k_3 on$	0.33973
$k_3 off$	176.66
$k_4 on$	0.00081002
$k_4 off$	0.00039542
$k_5 on$	0.0066125
$k_5 off$	0.0012099
$k_6 on$	0.90001
$k_6 off$	0.0010003
$k_7 on$	928.72
$k_7 off$	0.00010954
$k_8 on$	0.33973
$k_8 off$	176.66

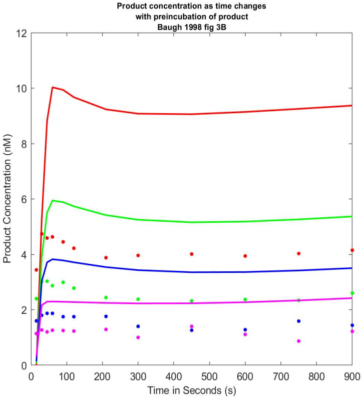
Changing k_{cat} to 7

Error = 0.23767

k_1^{on} = 0.49227 [0.029412,1] and k_3^{off} = 499.7685 [100,500]

k_7^{on} = 513.6591 [100,1000] and k_7^{off} = 0.00077161 [0.0001,0.001]





$k_{cat} = 7$

parameter	value
K_M	238
$k_1 on$	0.49227
$k_1 off$	110.16
K_{cat}	7
$K_{E,P}$	520
$k_3 on$	0.96109
$k_3 off$	499.77
$k_4 on$	0.0009
$k_4 off$	0.00036
$k_5 on$	0.00734
$k_5 off$	0.0011
$k_6 on$	0.0009
$k_6 off$	0.00036
$k_7 on$	513.66
$k_7 off$	0.00077161
$k_8 on$	0.96109
$k_8 off$	499.77